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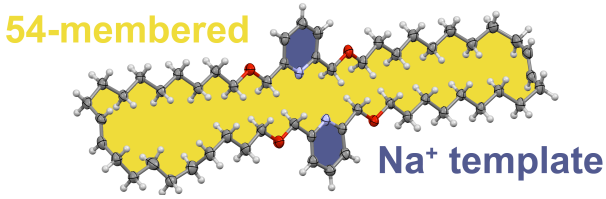

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Sodium template synthesis of a 54-membered bis(pyridine) macrocycle

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ABSTRACT

An operationally simple and high yielding sodium-template-based synthesis of a large bis(pyridine)-based macrocycle is described. Complexation of two equivalents of 2,6-bis(10-undecen-1-oxymethyl)pyridine with Na[BAr$^F_4$] (Ar^F = 3,5-$C_6H_3(CF_3)_2$) enabled the selective cross-metathesis of the terminal alkene substituents and formation of the corresponding bis(pyridine) macrocycle in 51% isolated yield. The new 54-membered macrocycle was characterised in the solid-state by X-ray diffraction in addition to verification of the structure in solution by NMR spectroscopy and ESI-MS.

1. Introduction

Since the seminal work by Pedersen in the 1960s, metal templates have been widely employed in macrocyclization reactions, with alkali and alkaline earth metal cations being notable for their use in the preparation of ethylene glycol-based crown ethers.[1] With interesting applications in the construction of molecules with interlocked topologies, methodologies involving transition metal templates and chelating heteroatom ligands have become commonplace in supramolecular chemistry.[2] For these applications nitrogen-based precursors, such as bipyridine-, phenanthroline-, and bis(imino)pyridine-based ligands, are generally preferred. Mixed nitrogen-oxygen donor ligands, such as 2,6-bis(alkenyl-oxy-methyl)pyridines, are readily accessible and potentially useful building blocks for the construction of large macrocyclic systems *via* olefin metathesis. Indeed, using elaborate tri- and hexa-nuclear platinum templates together with cross-metathesis, massive tris(pyridine) and hexa(pyridine) cyclic systems have been prepared solely through coordination of the pyridine group.[3] As part of their investigation of transition-metal-based molecular gyroscopes, Gladysz and co-workers have similarly exploited pyridine coordination to a single platinum center to prepare bis(pyridine) macrocycles through olefin cross-metathesis of 2,6-bis(2-propen-1-oxymethyl)pyridine and 2,6-bis(3-buten-1-oxymethyl)pyridine however, the cross-metathesis steps are low yielding (10% and 22%, respectively).[4] Motivated by the potential for tridentate coordination and operational simplicity, we postulated that such bis(pyridine) macrocycles could be alternatively prepared using alkali metal templates and herein report a straightforward and high yielding sodium-template-based synthesis of 54-membered bis(pyridine) macrocycle **3** from 2,6-bis(10-undecen-1-oxymethyl)pyridine **1**.

2. Results and discussion

The alkene functionalized pyridine **1** was readily obtained from reaction of sodium 10-undecen-1-oxide with commercially available 2,6-bis(bromomethyl)pyridine in 73% isolated yield. Full details are provided in the ESI along with the preparation and solid-state structure of **1**·MeI. In anhydrous CD_2Cl_2 the interaction of **1** with vigorously dried Na[BAr$^F_4$] (Ar^F = 3,5-$C_6H_3(CF_3)_2$)[5] resulted in dissolution of the otherwise insoluble salt along with a significant downfield shift of the pyCH_2O resonances (ca. 0.16 ppm) and concomitant upfield shift of the 3-pyridyl ^{1}H resonances (ca. 0.17 ppm). The system was observed to be under fast exchange at 298 K (400 MHz) and a 2:1 coordination stoichiometry, consistent with adoption of an octahedral geometry about the sodium cation, was established through a Job plot analysis (Figure 1). Complexation persisted in the gas-phase, with a signal at *m*/*z* +909.727 (37%) observed by ESI-MS for the intact parent cation (calc. 909.742), alongside the 1:1 adduct (*m*/*z* 466.357; calc. 466.366; 100%) and protonated ligand (*m*/*z* 444.374; calc. 444.384; 17%). Treatment of [Na(**1**)$_2$][BAr$^F_4$] prepared *in situ* with Grubbs I (15 mol%/**1**) under a slow stream of argon resulted in complete cross-metathesis of the terminal alkene groups after 20 h. In the absence of a sodium template, metathesis of **1** with Grubbs I principally resulted in ring closing metathesis, although small amounts of **2** were detected by ESI-MS. The sodium template and residual catalyst were removed by addition of HCl, neutralization with triethylamine and purification by flash column chromatography (silica gel; pentane:Et_2O, 1:1) to afford 54-membered **2** in 51% isolated yield.

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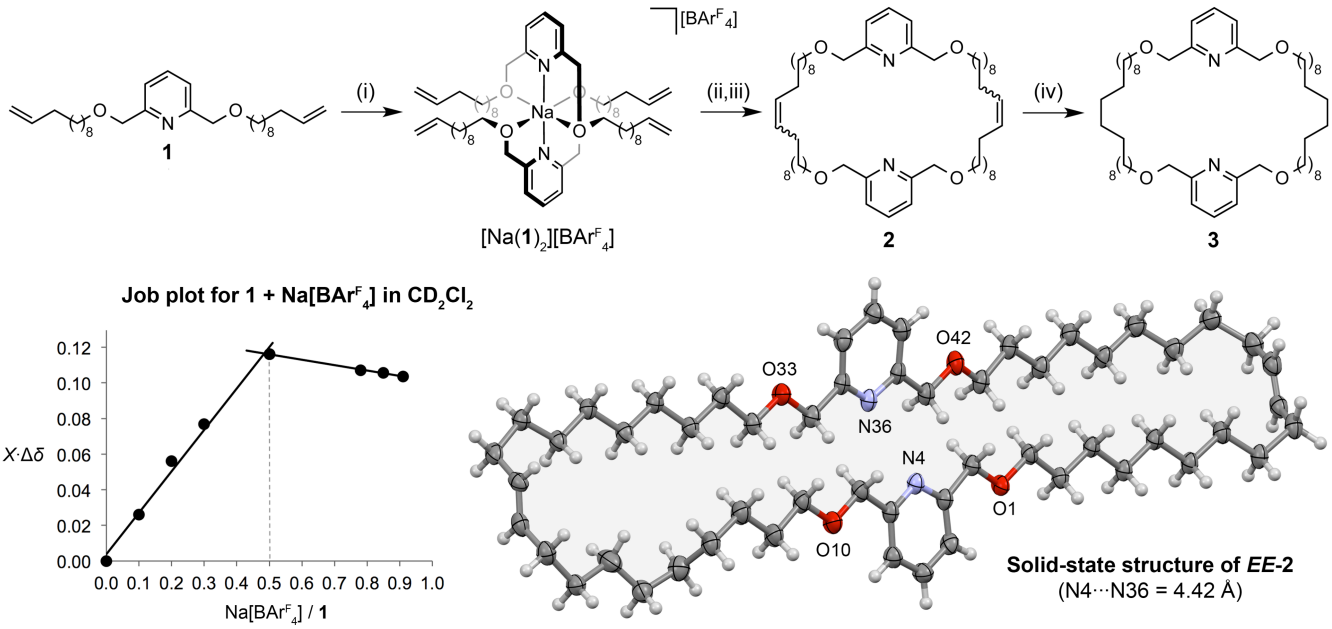

Figure 1. Sodium-template-based synthesis of **3** (above), Job plot for the reaction of **1** with Na[BAr^F_4] in CD_2Cl_2 (bottom left) and solid-state structure of *EE*-**2** (below right; thermal ellipsoids at 50% probability, minor disordered component omitted for clarity).[6] Reagents and conditions: (i) 0.5 equiv. Na[BAr^F_4], CH_2Cl_2, 293 K; (ii) Grubbs I (15 mol%/**1**), [complex] = 0.002 M, CH_2Cl_2, 293 K, 20 h; (iii) HCl then Et_3N (51% yield of **2** over 3 steps); (iv) Wilkinson's catalyst (10 mol%), H_2 (1 atm), toluene, 323 K, 20 h (quantitative yield).

Analytically pure macrocycle **2** was obtained as mixture of *EE*/*EZ*/*ZZ*-isomers that could not be separated on a preparative scale, despite repeated efforts. A small number of single crystals of (primarily) *EE*-**2** were obtained by recrystallization from CH_3CN/Et_2O which enabled the collection of X-ray crystallographic data.[6] The solid-structure of *EE*-**2** exhibits a peculiar rectangle-shaped conformation, with the short edge comprised of the internal alkenes and the pyridine groups adopting an offset head-to-head orientation (Figure 1, bottom right). To reaffirm the purity, macrocycle **2** was hydrogenated to give the corresponding saturated alkyl macrocycle **3** as the sole product (verified by high field ^1H and ^{13}C NMR spectroscopy) in quantitative yield.

Recently sodium-ion-based template strategies have begun to be successfully employed in the capture of interlocked systems.[7] In the absence of additional directing interactions, such as π-stacking,[8] the hydrocarbon pyridine arms in [Na(**1**)$_2$][BAr^F_4] are, however, unlikely to be held in the correct orientation for the formation of two interlocked macrocycles. Selective ESI-MS/MS fragmentation of the signal $[\mathbf{3}\cdot 2H]^{2+}$ in the ion trap of the spectrometer leads to peaks for $[C_{27}H_{48}NO_2]^+$ (*m/z* 418.369; calc. 418.369; 100%) and $[C_{27}H_{46}NO_2]^+$ (*m/z* 416.355; calc. 416.353; 50%) as the major ions. The significant presence of the higher molecular weight fragments with two pyridine groups ($[C_{34}H_{57}N_2O_4]^+$ *m/z* 557.435; calc. 557.431; 8%) and two alkyl chain arms ($[C_{47}H_{88}NO_3]^+$ (*m/z* 714.677; calc. 741.676; 13%) reaffirms the formulation of **3** (and **2**) as a 54-membered macrocycle rather than a [2]catenane alternative.

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Supplementary Material

Full experimental details, including the preparation and solid-state structure of **1**·MeI. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre (CCDC 1062644, **1**·MeI; 1062645, *EE*-**2**; 1062646, *EE*-**2** polymorph) and can be obtained free of charge via www. ccdc.cam.ac.uk/data_request/cif.

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solved with SIR92 (Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M. C.; Polidori G.; Camalli, M. *J. Appl. Cryst.* **1994**, *27*, 435) and refined by full-matrix least squares on F^2 using CRYSTALS (Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, K.; Watkin, D. J. *J. Appl. Cryst.* **2003**, *36*, 1487; Parois, P.; Cooper, R. I.; Thompson, A. L. *Chem. Cent., in press*). A small amount of *EZ*-**2** (34%) co-crystallized in the sample and resulted in apparent *cis*/*trans*- disorder of one of the double bonds, which was modeled with restraints to maintain the sensible geometries. All non-hydrogen atoms were refined with anisotropic displacement parameters; hydrogen atoms were generally visible in the difference map and treated in the usual manner (Cooper, R. I.; Thompson, A. L.; Watkin, D. J. *J. Appl. Cryst*. **2010**, *43*, 1100–1107). A second disorder free polymorph disorder was also observed (*EE*-**2**), with half a molecule in the asymmetric unit. The crystal was of particularly poor quality and the resulting data were found to be very noisy, nevertheless, the structure is included for completeness.

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